HETEROCYCLIC COMPOUND DERIVATIVES AND MEDICINES

TECHNICAL FIELD

The present invention relates to a novel heterocyclic derivative which is useful as a medicine, or a salt thereof, and a PGI_2 receptor agonist containing the same as an active ingredient.

BACKGROUND ART

Prostaglandin I_2 (PGI_2) is produced from arachidonic acid via prostaglandin H_2 (PGH_2) in the living body and has various potent pharmacological effects such as inhibition of platelet aggregation, vasodilation, inhibition of lipid deposition, and inhibition of leucocyte activation. It is therefore considered that PGI_2 is effective for treatment of peripheral vascular diseases (for example, arteriosclerosis obliterans, intermittent claudication, peripheral arterial embolism, vibration disease, and Raynaud's disease), systemic lupus erythematosus, reocclusion or restenosis after percutaneous transluminal coronary angioplasty (PTCA), arteriosclerosis, thrombosis, diabetic neuropathy, diabetic nephropathy, hypertension, ischemic diseases (for example, cerebral infarction and myocardial infarction), transient ischemic attack and glomerulonephritis, or acceleration of angiogenesis in peripheral blood vessel reconstruction technique or angiogenesis therapy.

However, PGI_2 is not suited for use as a medicine because it is chemically unstable and has very short biological half-life, and also has such a problem that side effect is likely to arise because it is difficult to separate the desired effect from the other effect. For the purpose of persistence of drug efficacy, relief of side effect and improvement of compliance, long acting preparations of prostaglandins have been researched and developed. However, satisfactory results have never been achieved.

Under these circumstances, it is expected that a PGI_2 receptor agonist, which is non-prostanoid and has excellent affinity to PGI_2 receptor and chemical stability, exerts excellent therapeutic effect a medicine as compared with conventional PGI_2 preparations, and thus it has intensively been researched and developed.

For example, it has been known that imidazole derivatives (Br. J. Pharmcol., 102, 251 (1991)), oxazole derivatives (J. Med. Chem., 35, 3498 (1992), J. Med. Chem., 36, 3884 (1993)), pyrazole derivatives (Folia Phermacol. Jp., 106, 181 (1995), Bioorg. Med. Chem. Lett., 5, 1071 (1995), Bioorg. Med. Chem. Lett., 5, 1083 (1995)), pyrazinone derivatives (Bioorg. Med. Chem. Lett., 10, 2787 (2000)) and oxime derivatives (Folia Phermacol. Jp., 106, 181 (1995), Bioorg. Med. Chem. Lett., 5, 1071 (1995), Bioorg. Med. Chem. Lett., 5, 1083 (1995)) have PGI_2 receptor agonistic activity.

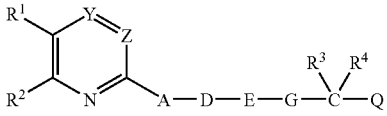
Also it is known that 2,3-diphenylpyrazine derivatives (Japanese Unexamined Patent Publication No. Hei-7-33752) have a herbicidal effect, 2,3-diphenylpyridine derivatives and 5,6-diphenylpyrimidine derivatives (WO92/01675) have a leukotriene B_4 antagonism and 2,3-diphenylpyridine derivatives (WO96/18616) have a nitric oxide synthesis inhibitory effect. However, it is not known that these compounds have a PGI_2 receptor agonistic activity.

DISCLOSURE OF THE INVENTION

An object of the present invention is to provide a novel PGI_2 receptor agonist and a novel heterocyclic derivative.

To achieve the above object, the present inventors have synthesized various compounds during the process of study and found that heterocyclic derivatives represented by the following general formula (1) (hereinafter also referred to as heterocyclic derivatives (1)) have excellent PGI_2 receptor agonistic activity, and thus the present invention has been completed.

(1)



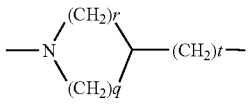
wherein R^1 and R^2 are the same or different and each represents an optionally substituted aryl, and the substituents are the same or different and 1 to 3 substituents are selected from the group consisting of halogen, alkyl, haloalkyl, arylalkyl, alkoxy, alkylthio, alkoxyalkyl, alkylsulfonyl, hydroxy, amino, monoalkylamino, dialkylamino, carboxy, cyano and nitro,

Y represents N, N→O or CR^5, Z represents N or CR^6; and R^5 and R^6 are the same or different and each represents hydrogen, alkyl or halogen,

A represents NR^7, O, S, SO, SO_2, or ethylene, and R^7 represents hydrogen, alkyl, alkenyl or cycloalkyl,

D represents alkylene or alkenylene which are optionally substituted with hydroxy, or A and D are combined with each other to form a divalent group represented by the following formula (2):

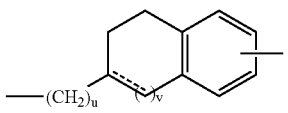
(2)



r represents an integer of 0 to 2, q represents an integer of 2 to 3, and t represents an integer of 0 to 4,

E represents phenylene or single bond, or D and E are combined with each other to form a divalent group represented by the following formula (3):

(3)



(═══ represents single bond or double bond.)

u represents an integer of 0 to 2, and v represents 0 or 1,

G represents O, S, SO, SO_2, or $C(R^8)(R^9)$, and R^8 and R^9 are the same or different and each represents hydrogen or alkyl,

R^3 and R^4 are the same or different and each represents hydrogen or alkyl,

Q represents carboxy, alkoxycarbonyl, tetrazolyl, carbamoyl, monoalkylcarbamoyl, dialkylcarbamoyl, or a group represented by the following formula (22):